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PERSPECTIVE

Iridium catalysis: application of asymmetric reductive hydrogenation

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Iridium, despite being one of the least abundant transition metals, has known several uses. N,P-ligated iridium catalysts are used to perform many highly selective reactions. These methodologies have been developed extensively over the past 15 years. More recently, the application of iridium N,P catalysts in asymmetric hydrogenation has been a focus, to find novel applications and to expand on their current synthetic utility. The aim of this *perspective* is to highlight the advances made by the Andersson group.

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Introduction

The field of catalysed asymmetric hydrogenation is well known and has been actively investigated for over four decades. In 2001 the Nobel Prize in Chemistry was awarded to Noyori (BINAP)¹ and Knowles (DIPAMP) for their work in catalysis.²

Historical development

Discovered in 1804 by Smithson Tennant, iridium is amongst the least abundant elements in the Earth's crust.³ It knew little use until the synthesis by Vaska of his eponymous complex:⁴ [IrCl(CO)(PPh₃)₂] (Figure 1.a), a catalyst of the [L3MX]-type.⁴ Following parallel development with other platinum group metals, Shrock and Osborn (Figure 1.d) discovered that an [L₄Rh]⁺X[−] complex could convert in situ to an [L₂Rh]⁺X[−] active catalyst. Overall having a 2:1 mono-dentate ligand/metal ratio was superior to the previously employed 3:1, since it removes the need to extrude a phosphine group during the catalytic cycle.⁵ In turn, this discovery was carried across to iridium by Crabtree, leading to the synthesis of what is now known as Crabtree's catalyst: [(COD)Ir(PCy₃)(C₅H₅N)]PF₆ (Figure 1.c).⁶ This catalyst was able to hydrogenate hexene and cyclohexene as well as compounds containing tetra substituted double bonds.⁷ The latter had displayed very poor rates of reaction with most platinum group catalysts of the time.

Replacing two small mono-dentate ligands by a larger chiral bi-dentate one opens the possibility for asymmetric hydrogenation, as the chirality can be more efficiently transferred to the product from the ligand. Kagan's DIOP ligand⁸ and the aforementioned DIPAMP, developed by Knowles for the L-DOPA process (based on Wilkinson's catalyst) are amongst the most famous examples of this. Similarly, the optimisation of N,P-ligated iridium complexes lead Pfaltz to publish in 1998 a new catalyst, a chiral analogue to Crabtree's, using a PHOX type

Figure 1. Evolution of catalysts for hydrogenation and their ligands.

ligand to bind to the metal. This discovery birthed the field of iridium catalysed asymmetric hydrogenation, and his group has since remained at the forefront of the field.⁹ Further improvements to the performances of the catalysts were achieved by replacing the previous counter anion (PF_6^-) with a less coordinating one: BArF (*Tetrakis* [3,5*bis*(trifluoromethyl) phenyl]borate).¹⁰ In the past 15 years, iridium catalysed asymmetric hydrogenation has undergone tremendous development, both using NP-ligands¹¹ and others.¹²

Platinum group catalysed asymmetric hydrogenation

Rhodium and ruthenium have been applied successfully to many applications since the seminal works of Knowles and Noyori. The “privileged ligands”, such as BINAP, DIPAMP and DIOP, have acquired this nickname due to their versatility and routine use for a large variety of compounds.¹³ However the unifying flaw of both Rh and Ru catalysts is the necessity to have a proximal coordinating group, generally a carbonyl derivative. Halpern determined the mechanism by which a P,P ligated rhodium catalyst asymmetrically reduces a double bond (Scheme 1).¹⁴ In this case, the chirality of the ligand is imparted onto that of the substrate (ie. an *R* ligand generates an *R* product). The efficiency of the chirality transfer comes from the bi-dentate substrate binding, through both the π -bond and the proximal donor atom (O or N) to the metal centre, guided by the chiral ligand.

Scheme 1: Rhodium catalysed asymmetric hydrogenation.

Conversely, the iridium catalyst is able to hydrogenate the substrates, in high enantioselectivity without any such coordinating group, owing to its mono-dentate binding mode. In this case the sheer steric bulk of the ligand is the source of the chirality for the product. Several DFT studies have been conducted, to probe the nature of the catalytic cycle (Scheme 2). Two have been proposed, and share the same active Ir(III) complex, but differ in the ensuing pathway. Chen¹⁵ and Pfaltz^{11a} propose an overall Ir (I/III) cycle, where the solvent coordinates principally to the metal centre, whereas Andersson published a (III/V) mechanism where hydrogen binds in greater amount to the iridium, displacing the solvent from the coordination site (Scheme 2).¹⁶ A similar DFT study was conducted by Burgess for an N_3C -ligated complex and also points toward an Ir (III/V) process.¹⁷ Due to the similarity of the two proposed cycles and

the difficulty to detect the intermediates *in situ*, neither has been disproved yet, as they provide hints but no definite evidence.

Scheme 2. Iridium catalysed asymmetric hydrogenation, using a bidentate N,P-ligand. A. formation of the active catalyst. B & C. Proposed catalytic cycles. (N.b. for the sake of clarity, the counter anion and the charge were omitted)

Ligand design and optimisation

Figure 2. N,P-ligands employed in this paper.

Catalysts and their ligands are not *one size fits all*. The different properties of a substrate (size and arrangement of substituents, electrophilicity of the alkene bond) will make it more or less compatible with the different catalysts. As can be seen from figure 2, a variety of catalysts have been designed. They share a common N,P-backbone, but with many small differences. The size of the library results from fine tuning the ligands for the selected substrates.

The quadrant selectivity model

With N,P-ligated iridium catalysts, the enantio-selectivity stems from the bulk of the chiral ligand. A quadrant model was devised to rationalise and also predict the configuration of the resulting product. As shown in Figure 3, the iridium centre is surrounded by two bulky groups that generate steric hindrance towards the alkene. The heterocycle bears a group (often phenyl), pointing out of the plane, which generates a large bulk in the plane of the coordinated olefin, *trans* to the phosphine: the hindered quadrant. The di-aryl phosphine, while large, has only a small portion of its bulk coming out of the plane: the semi hindered quadrant (in this example, the larger of the Ph ring). The other two quadrants are relatively free at the coordination site (though for ligands **C** and **F**, any rear access to the open quadrant is blocked by the bulk of the bicycle). An increase in size of the heterocycle's substituent group or of the phosphine aryl can be beneficial: a smaller reaction pocket means a tighter fit, however it engenders the risk of generating too small a reaction site in which case the extra steric bulk will cause a drop in both yield and *ee* as the substrate is unable to fit properly.

Figure 3. Quadrant selectivity model for the asymmetric reduction of alkenes.

Heterocycle tuning

The versatility of the N,P ligand class comes from the possibility of tuning the separate groups within the catalyst to obtain the optimal result. The heterocycle will have a great impact on the electrophilicity of the iridium centre. A more electron rich, basic

heterocycle will transfer more electron density to the iridium. Conversely, the oxazole is a very weak base, with a lesser donation electron density to the iridium making it a better electron acceptor for a richer alkene. The basicity of the nitrogen in these aza-cycles depends on the second heteroatom as well as on the saturation of the ring (Figure 4). The importance of the acidity of the solution and the catalyst was probed, and showed that Ir catalysts are significantly more acidic than their Rh counterparts. It transpired from the study that as the electron density at the iridium increased, the hydride became less acidic, and conversely electron withdrawing groups on the iridium increase their acidity.¹⁸

Another small effect, linked to the choice of the second heteroatom (N, O or S) will be the size of the ring. A sulphur, by its larger radius will distort the ring and push the substituent further inwards thus reducing the size of the reactive pocket enabling higher *ee* which can in turn restrict the alkene's access to the iridium.

Figure 4. Basicity of aza-cycles, used in N,P ligands.

Substrate classes

Iridium catalysts show a great versatility in the scope of the olefins they are able to hydrogenate. This section aims to showcase this adaptability of the catalysts by focussing on different substrate classes. Non-functionalised olefins that are unable to be asymmetrically hydrogenated using other platinum group metal catalysts, will be discussed first. Then bulky 1,1-di- and 1,1,2-tri-aryl substituted alkenes, followed by electron rich vinylic enol phosphates, then electron deficient fluorinated olefins, strongly coordinating alkene phosphonates, esters, and finally heterocyclic compounds.

Non-coordinating olefins

As discussed in the introduction, iridium is able to perform asymmetric hydrogenation of non-functionalised olefins. However where Crabtree's catalyst gave racemic products, chiral

analogous bi-dentate N,P-ligands were able to perform very well. Following on the works of began by Pfaltz,¹⁰ Källström¹⁹, then by Hedberg²⁰ and Li²¹ the performances of this series of new ligands were evaluated for a selection of substrates, as can be seen in Table 1.

The non-functionalised olefins, especially *trans*-methylstilbene (entry 1), have remained a mainstay for the testing of new catalysts. It presents several advantages as a model substrate: it is readily available as a pure isomer; the olefinic bond is fully conjugated; it is a strong chromophore; the racemate separates easily by chiral HPLC and as a *trans*-isomer it fits well in the quadrant model. Similar compounds such as entry 2 and 3, gave very comparable yields and *ees*. The most surprising feature is the difference in selectivity between entries 5 and 6. A small change, the removal of the distal methoxy group upset the electronics of the olefinic bond, which resulted in a drastic drop in *ee*. Similarly, by moving the methyl just one carbon further on the cycle (entries 6 and 7) lead to a restoration of the high *ee*, though by forming the opposite enantiomer (change from *R* to *S*).

Table 1. Hydrogenation of non-functionalised olefins.

Entry	Substrate	Ligand	conv.	<i>ee</i>
1		A	>99	>99 (<i>S</i>)
		B	45	97 (<i>R</i>)
		C	>99	>99 (<i>S</i>)
2		C	>99	>99 (<i>S</i>)
3		A	>99	89 (<i>S</i>)
		B	>99	>99 (<i>R</i>)
		C	>99	>99 (<i>S</i>)
4		A	>99	95 (<i>S</i>)
5		A	>99	99 (<i>R</i>)
		C	>99	>99 (<i>R</i>)
6		B	>99	83 (<i>S</i>)
		C	>99	55 (<i>R</i>)
7		A	>99	98 (<i>S</i>)

Conditions: 30-50 bars H₂, room temperature, [LrCOD]BARF (0.5%) ligands as indicated, for 2 hours, in freshly distilled CH₂Cl₂ as 0.25M solution. Conversion and *ee* in %. Conversion determined by H¹NMR spectroscopy and *ee* determined by Chiral HPLC.

1,1-Diaryl and 1,1,2-triaryls

The diaryl methine moiety constitutes an important centre of chirality in many natural organic molecules (e.g. podophyllotoxin²² and in the synthesis of pharmaceuticals (e.g. sertraline²³ and tolterodine²⁴). Sertraline in particular, known under the trade names *Zoloft* and *Lustral*, is a very high selling anti depressant.²⁵ While ruthenium has been used in this process for 1,4-addition, sometimes in good enantioselectivities, the substrate scope remains small overall.²⁶ Similarly, Rh catalysts have been used, to obtain diarylethanes, but again the substrate scope was limited.²⁷ The application of asymmetric hydrogenation to these substrates was highly successful as shown

in Table 2.²⁸

As can be seen, most substrates required higher pressure and temperature than commonly used. This in turn require often changing from the normally employed solvent (CH₂Cl₂) to α,α,α -trifluoro-toluene, which exhibits very similar electronic properties to dichloromethane but with a higher boiling point.²⁹ As part of the screening process it was determined that either an increase in temperature (from 25 to 40°) or pressure (50 to 100 bar) was necessary, though when one sufficed an elevation of pressure was preferred over that of temperature (which caused a decrease in *ee*).

It should be noted that the nature of the third substituent had very little impact on either *ee* or conversion as can be inferred from the comparison of entries 1 to 3. While the *para*-substituent on the aromatic ring was changed, entry 3 and 5 show that a switch from *E* to *Z* starting materials lead to a switch in enantiomers, which is likely to be an expression of the change in chirality of the products: *E* starting material are predicted to yield an *S* product, and conversely *Z* an *R* product.

Table 2. Hydrogenation of di- and tri-aryl olefins

Entry	Substrates	conv.	<i>ee</i>	Ligand	Solvent
1		>99	>99 (-)	B	CH ₂ Cl ₂
2		>99	>99 (+)	B	CH ₂ Cl ₂
3		>99	97 (-)	F1	PhCF ₃
4		>99	95 (<i>S</i>)	F1	PhCF ₃
5		99	99 (+)	F1	PhCF ₃

Conditions: 50-100 bars H₂, room temperature, [LrCOD]BARF (0.5-1%) ligands as indicated, for 24 hours, in freshly distilled CH₂Cl₂ as 0.25M solution. Conversion and *ee* in %. Conversion determined by H¹NMR spectroscopy and *ee* determined by Chiral HPLC.

Vinyl phosphines and phosphonates oxides

Phosphonates and phosphine oxides are highly coordinating groups, and their vinyls should make for good substrates for Ru and Rh catalysis. However these substrates have received rather little attention: while there are reports of Chiraphos type ligands being synthesised by asymmetric hydrogenation,³⁰ in most cases they are generated by either stoichiometric amounts of enantiopure reagents or through the resolution of racemic mixtures.³¹ Organophosphorous compounds can be employed for a great variety of uses including ligands for catalysis and drugs.³² Since their use is mostly in chiral molecules, it is of vital importance to produce them in an optically pure form. Cheruku *et al* reported these hydrogenations in excellent conversion and *ees* for a variety of terminal substrates (Table 3).³³ From the small selection of aromatic 1,1-di-substituted compounds it transpires that the electron donating group perform similarly with electron

withdrawing ones (entries **4** and **6**). Less bulky non-aromatic substrates were also hydrogenated for excellent results. The reaction scope was broadened by expanding to a naproxen analogue (entry **9**) which produced very satisfactory results. Finally a small selection of strongly electron deficient tri-substituted vinyl-carboxy-ethyl-phosphonates was hydrogenated in equally high yields and *ees*. Interestingly both *E* and *Z* isomers gave the same isomer, a phenomenon also observed in the ruthenium-catalysed asymmetric hydrogenation of fluorinated olefins.³⁴ Why the *E* isomer is poorly reactive when alone, whereas the *E/Z* mixtures give excellent results remains unexplained.

Table 3. Hydrogenation of vinyl phosphines and phosphonate oxides

Entry		conv.	ee
1	Ph	>99	>99 (<i>R</i>)
2	<i>o</i> -tol	>99	>99 (+)
3	4-Me-Ph	>99	>99 (+)
4	4-OMe-Ph	>99	>99 (+)
5	4-F-Ph	>99	>99 (+)
6	4-CF ₃ -Ph	>99	99 (+)
7	Cy	>99	>99 (+)
8	Ph-(CH ₂) ₂	>99	>99 (+)
9		79	91
10	Ph <i>E</i>	<10	90 (+)
11	Ph <i>Z</i>	>99	>99 (+)
12	Ph <i>E/Z</i>	>99	>99 (+)
13	Bn <i>E</i>	>99	>99 (+)

Conditions: 30-50 bars H₂, room temperature, [**F1**IrCOD]BARf (0.5%) ligands as indicated, overnight, in freshly distilled CH₂Cl₂ as 0.25M solution. Conversion and *ee* in %. Conversion determined by ¹H NMR spectroscopy and *ee* determined by Chiral HPLC.

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Trifluoromethylated olefins

Trifluoromethylated compounds have known a variety of uses, which spread from pharmaceuticals to agrochemicals to liquid crystal display systems (LCD screen).³⁵ In the past, most methods of obtaining chiral tri-fluorinated compounds of this type revolved around the resolution of racemates or enantioselectively adding the CF₃ moiety to a chiral compound.³⁶ This moiety has a very strong effect on the electron density of the olefinic bond, more so than a carboxylic or ether group would.³⁷ The asymmetric hydrogenation of trifluoromethylated alkenes has been attempted with (*R*)-BINAP-Ru catalysts with results varying from racemic to 83% *ee*.³² Similarly, rhodium catalysis was used in conjunction with (*R,R*)DiPAMP or (*S,S*) Chiraphos, though

results remained capped at 77% *ee*.³⁸ As can be seen in Table 4, from results obtained in the Andersson group,³⁹ the hydrogenation of these substrates was achieved with very high conversion and *ees* (up to 96%). Vinyl fluorides have a similarly polarised olefinic bond, but when hydrogenated with similar N,P-ligated iridium catalysts and conditions, the results remained inferior to those in Table 4.⁴⁰ Following the reasoning outlined in the ligand design section, the tuning of the ligand was pivotal to obtaining good results, hence the use of highly similar catalysts. The choice of the N linker atom to the phosphine group combined with the choice of a thiazole heterocycle lead to a highly enantioselective iridium catalyst, which was able to hydrogenate with the electron poor alkenes efficiently. This demonstrates the importance of harnessing and matching the electronics of the olefin substrate.

Table 4. Hydrogenation of trifluoromethylated olefins

Ligand			
Entry	Substrate	conv.	ee
1		94	95 (-)
2		87	92(-)
3		88	96 (-)
4		4	n/a
5		56	83 (-)
6		85	95 (-)
7		96	74 (-)

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Conditions: 100 bars H₂, room temperature, [LrCOD]BARf (0.5%) ligands as indicated, for 72 hours, in freshly distilled CH₂Cl₂ as 0.25M solution. Conversion and *ee* in %, ligands employed: **1-6**, R= Ar = Ph; **7**, R= 3,5-diMePh and Ar= *o*-tol. Conversion determined by ¹H NMR spectroscopy and *ee* determined by Chiral HPLC.

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The reactivity of *E* and *Z* isomers was noted to be different in both iridium and ruthenium catalysis.⁴¹ The *E* and *Z* isomers reacted at very different rates, Table 4 entries **3-5** showing the extreme case: the *cis*- is almost unreactive whereas the *trans*- substrate gives near full conversion and high *ee*. It is worth noting that both *E* and *Z* isomers will give ground to the same enantiomer of the product, rather than opposite enantiomers as is normally observed for many other substrates. One might suspect that in this case, the strong polarisation of the double bond might override the substrate's steric preference.

Enol phosphinates

Due to their poor ability to coordinate to the metal during catalysis, enol ethers and enol phosphinates have been difficult to hydrogenate asymmetrically prior to the use of N,P-ligated iridium.⁴² Some earlier attempts to asymmetrically hydrogenate

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enol ethers were conducted using rhodium-DIOP catalysts with a variety of ligands: DIPAMP, DuPhos, KetalPhos and TangPhos.⁴³ Enamines and alkenes (strongly coordinating groups) are ideally hydrogenated with chiral-ligated rhodium or ruthenium catalysts. However from the results in Table 5, one would expect iridium to impose itself as the metal of choice for this class of substrates. The product of this hydrogenation can in turn be used as a building block in a more complex synthesis, for example undergoing cross coupling with boronic acids.⁴⁴

By using a bicyclic mimic of Pfaltz's catalyst (Ligand **F1**, see Figure 1) excellent results were obtained across a large section of both tri substituted and terminal di-substituted enol phosphinates. Very few examples yielded less than near full conversion. As noted in the original papers, the substitution on the aromatic group seemed to have little to no effect on the *ee* but does impact the rate of reaction. Electron withdrawing groups in the *para*-position of the phenylic substituent accelerated the reaction, in some cases a full conversion was obtained in as little as an hour, whereas electron donating groups slowed the reaction requiring often 3-4 hrs. This indicates that electronics play some role in the reaction, not just sterics. Entry **9** stands out with its comparatively low *ee*, of only 85%, this is due to the naphthyl group's much greater bulk compared to the other substituents on the list.

Table 5. Hydrogenation of enol phosphinate ethers

Entry	R	conv.	<i>ee</i>
1	Ph	>99	>95 (<i>R</i>)
2	4-Me-Ph	97	96 (<i>R</i>)
3	4- <i>t</i> -Bu-Ph	93	94 (<i>R</i>)
4	4-Br-Ph	>99	>99 (<i>R</i>)
5	4-CF ₃ -Ph	>99	99 (<i>R</i>)
6	4-NO ₂ -Ph	>99	92 (<i>R</i>)
7	Cy	>99	>92 (<i>R</i>)
8	<i>t</i> -Bu	>99	>99 (<i>R</i>)
9	2-naphthyl	>99	85 (<i>R</i>)

Conditions: 30 bars H₂, room temperature, [F1IrCOD]BARF (0.5%), overnight, in freshly distilled CH₂Cl₂ as 0.25M solution. Conversion and *ee* in %. Conversion determined by ¹H NMR spectroscopy and *ee* determined by Chiral HPLC.

The alkyl phosphinates were subsequently converted to alcohols using BuLi, and maintained their high enantiomeric excess. This served a twofold purpose: chiral alcohols are common building blocks in organic chemistry, and permitted the determination of absolute configuration by comparing the rotatory direction to literature values.

Esters

Chiral esters are common patterns found in a number of natural products, pharmaceuticals and fragrances.⁴⁵ The importance of the reaction can be derived from the number of attempts and competing methods devised to carry it out. Both copper and ruthenium have been employed in asymmetric reductions of α,β -unsaturated carbonyls,⁴⁶ however they are difficult reactions to

carry out due to the water sensitivity of the hydride donors.⁴⁷ This reaction was also conducted using enzyme catalysis, however the reaction was both slow and poor in yield.⁴⁸ Overall, a number of metal catalysed reactions have been studied to asymmetrically add both metallic and non-metallic reagents to α,β olefins, as was discussed in several reviews.⁴⁹ In the work by Li *et al.*,⁵⁰ iridium catalysts were used to hydrogenate unsaturated esters in full conversion and excellent selectivity, as can be seen in Table 6. Most notably, entry **9** is a key intermediate to a number of natural compounds and drugs,⁵¹ as are entries **5** and **10**.⁵²

Carbocycles and heterocycles

The importance of chiral heterocycles in nature cannot be overstated: they are present especially in drugs and natural molecules, making them highly relevant to organic chemists.⁵³ The asymmetric hydrogenation of 1- and 2- substituted piperazine and piperidines was conducted using both rhodium and ruthenium leading to high selectivities.⁵⁴ In the work by Verendel *et al.*, excellent enantio-selectivities were obtained for these homo- and hetero-cyclic alkenes, irrespective of the nature of the substituent, whereas the 2,3 unsaturated cycles benefited from electron withdrawing substitutions. Five membered rings of the same class proved more challenging and require further optimisation.

Table 6. Hydrogenation of vinyl esters

Substrate	Entry	<i>ee</i>
<i>E</i> 1	98 (<i>R</i>)
	<i>Z</i> 2	98 (<i>S</i>)
<i>E</i> 3	>99 (<i>R</i>)
	<i>Z</i> 4	98 (<i>S</i>)
5	98 (<i>R</i>)
6	97 (-)
<i>E</i> 7	>99 (-)
	<i>Z</i> 8	>99 (+)
9	>99 (<i>R</i>)
10	92 (<i>S</i>)

Conditions: 50 bars H₂, room temperature, [C1rCOD]BARF (0.5-1%) ligands as indicated, overnight, in freshly distilled CH₂Cl₂ as 0.25M solution. Full conversion was obtained for every substrate. Conversion determined by ¹H NMR spectroscopy and *ee* determined by Chiral HPLC.

The substrates were synthesised by a second-generation Grubbs catalyst mediated ring closing metathesis.⁵⁵ After preliminary investigation using principally 2-substituted azacycles, excellent results were obtained.⁵⁶ In Table 6, a selection of hydrogenated substrates is presented.⁵⁷

This method can be used, for example, to obtain the key

intermediate in the total synthesis of the drug Preclamol.⁵⁸ Further investigations into the use of substituted pyridines as a source of chiral piperidines by iridium catalysed asymmetric hydrogenation have been undertaken.⁵⁹

Table 7. Hydrogenation of substituted cyclic olefins

R	Entry	Ligand	conv.	ee
Me 1	F1	>99	>99 (-)
	Bn 2	F1	97	92 (-)
	Ph 3	B	>99	>99 (+)
	4-Me-Ph 4	B	>99	>99 (+)
4-Cl-Ph 5	E	94	98 (-)
R ¹ = Ph 6	D	>99	98 (-)
	R ² = H 7	D	>99	96 (-)
R ¹ = H 8	B	>99	>99 (+)
	R ² = Ph 9	B	48	>99 (-)
	R ² = Ph 10	B	>99	>99 (+)
Ph 11	D	99	99 (-)
	Me 12	D	99	93 (-)

Conditions: 30-100 bars H₂, room temperature, [LrCOD]BArF (0.5-1%) ligands as indicated, overnight, in freshly distilled CH₂Cl₂ as 0.25M solution. Conversion and *ee* in %. Conversion determined by ¹H NMR spectroscopy and *ee* determined by Chiral HPLC.

Synthesis of chiral building blocks through asymmetric hydrogenation

While the focus of the Andersson group is methodology development, the application of said methodologies is important to give tangible examples of their usefulness. In this section, the combinations of asymmetric hydrogenation with named reactions to give novel pathways to building blocks and processes are discussed.

Chiral olefinic hydrocarbons via asymmetric hydrogenation and the Ramberg-Bäcklund reaction

Inspired by the successes in the asymmetric hydrogenation of the aza-cyclic olefins, cyclic sulphones were evaluated.⁶⁰ Not only are chiral sulphone moieties found within drugs and their precursors,⁶¹ but also the sulphone group can be eliminated to form new olefins such as *via* the Ramberg-Bäcklund reaction,⁶² as well as in the Julia olefination.⁶³ The asymmetric hydrogenation destroys a functional group (π -bond) to generate the centre of chirality, however the olefination regenerates one in a nearby position thus maintaining a functional group, to allow further synthetic usage. As can be seen in Table 8, very good conversions and *ees* were obtained for many cyclic substrates. Also, following the Ramberg-Bäcklund reaction, there was no loss of *ee* observed in any of the studied compounds.

In the wake of the excellent results obtained with the cyclic

sulphones, acyclic sulphones were also screened.⁶⁴ Vinylic and allylic sulphone compounds were hydrogenated and afforded very good *ees*, as can be seen in Table 9.

Table 8: Hydrogenation of cyclic sulphones

		Hydrogenation		Ramberg-Bäcklund	
R	Entry	Ligand	conv.	ee	Conversion
Me 1	F2	>99	96 (S)	>99
	Ph 2	C	>99	98 (R)	88
	4-Me-Ph 3	C	>99	96 (R)	85
	4-OMe-Ph 4	C	>99	97 (-)	90
	CH ₂ OH 5	C	>99	92 (-)	82
6	C	43	90 (R)	30
Me 7	F2	>99	89 (+)	>99
	Ph 8	C	>99	90 (S)	89
	CH ₂ OH 9	C	>99	90 (S)	90

Hydrogenation conditions: 50 bars H₂, room temperature, [LrCOD]BArF (0.5%) ligands as indicated, overnight, in freshly distilled CH₂Cl₂ as 0.25M solution. Ramberg-Bäcklund conditions: *t*BuOH/CH₂Cl₂, Al₂O₃/KOH, CF₂Br₂, 2 hours, 0°C. Conversion determined by ¹H NMR spectroscopy and *ee* determined by Chiral HPLC.

Different sulphone substituents were used in place of the Bn in the allylic sulphone (Table 9, entry 5). Unfortunately the (synthetically most useful) heterocycles gave no conversion, presumably through competitive binding to the metal, due to their similarity to the ligand (entries 6 and 7). The benzyl group gave the best *ees* for vinylic

Table 9. Hydrogenation of acyclic vinyl and allyl sulphones

		Hydrogenation		Ramberg-Bäcklund	
R	Entry	conv.	ee	Conversion
Ph 1	>99	96 (S)	91	
	4-OMe-Ph 2	>99	92 (+)	93	
	4-Br-Ph 3	>99	96 (+)	94	
	<i>n</i> -Bu 4	>99	93 (R)	78
5	>99	97 (-)	75	
	6	0	-	-	
	7	0	-	-	

Hydrogenation conditions: 50 bars H₂, room temperature, 0.5% catalyst, [CfCOD]BArF (0.5%), 17 hours, in freshly distilled CH₂Cl₂ as 0.25M solution. Ramberg-Bäcklund conditions: *t*BuOH/CH₂Cl₂, Al₂O₃/KOH, CF₂Br₂, 2 hours, 0°C. Conversion determined by ¹H NMR spectroscopy and *ee* determined by Chiral HPLC.

Unlocking the third dimension of benzene: asymmetric hydrogenation coupled with Birch reduction

Scheme 3 Arrangement of the non-conjugated double bonds in the Birch product, based on the nature of the substituent.

Both well understood and known, the Birch reaction consists of the reduction of a mono- or poly- substituted benzene ring to the corresponding non-conjugated 1,4-cyclohexadiene.⁶⁵ As can be seen in Scheme 3, this reduction is regioselective, based on the electron donating or withdrawing nature of the substituents. This high versatility leads to its common use in natural product synthesis.⁶⁶ However there are yet only two reports of asymmetric hydrogenation combined with the Birch reduction, to apply two consecutive reductions to the same core.⁶⁷ As shown in Table 10, good yields and excellent *ees* were obtained.

Scheme 4. Successive reductions of substituted naphthalene. Reaction conditions: a. Li, NH₃, EtOH, 93%. b. [BIrCOD]BARF (0.5%), H₂ (20 bar), CH₂Cl₂, 18 hours, 72%, *ee* (*trans*) 99%. c. RuCl₃·H₂O, NaIO₄, 54%.

Additionally, the asymmetric nature of the iridium reduction of two π -bonds meant that there was a reinforcement of the *cis:trans* ratio. As can be seen from the table, *trans*- products are favoured over *cis*- ones, also this would indicate a dissociation of the substrate from the catalyst after the hydrogenation of the first double bond. As the first double bond is hydrogenated, a steric bulk is introduced to one face of the molecule, rendering it harder to access and thus enhancing the excess of *trans*- over *cis*- products, and a higher *ee* in the *trans*- while decreasing the *ee* of the *cis*- product.

The scope of this consecutive reduction method was expanded to 2,7-dimethoxynaphthalene, which in addition to being hydrogenated with excellent selectivities (*trans:cis* ratio: >99:1, *ee*: 99%), was subsequently opened to form a chiral decacycle (Scheme 4).

Table 10: Results of the Birch then asymmetric reductions of starting benzenes.

R ¹	R ²	R ³	Entry	Ligand	yield (%)		ratio		<i>ee</i> (%)	
					II	III	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>
OMe	OMe	H	1	E	65	56	>99	<1	>99	-
OMe	CH(OH)Bu	H	2	B	70	81	83	17	98	62
OMe	CH(OH)Ph	H	3	B	82	84	78	22	>99	60
OMe	<i>i</i> -Bu	H	4	B	52	68	82	18	98	66
<i>i</i> -Pr	<i>i</i> -Pr	H	5	E	45	76	75	25	>99	-

Birch conditions: Na, NH₃, *t*-BuOH or EtOH, 0°C, 6 hours.

Hydrogenation conditions: 20 bars H₂, room temperature, [LIrCOD]BARF (0.5%) ligands as indicated, 18 hours, in freshly distilled CH₂Cl₂ as 0.25M solution. Conversion determined by ¹H NMR spectroscopy and *ee* determined by Chiral HPLC

Conclusion

In conclusion, asymmetric hydrogenation by way of N,P-ligated iridium catalysts has shown itself to be a versatile method. Research has shown that by slightly adapting the ligand to the target, excellent results could be obtained for a large variety of substrates. Additionally, the more recent work combining the highly selective asymmetric hydrogenation along with other known reactions show that it is a useful tool in the synthetic chemist's toolbox.

Biography

Pher G. Andersson was born 1963 in Växjö, Sweden. He was educated at Uppsala University where he received his BSc in 1988 and his PhD in 1991. After postdoctoral research at Scripps Research Institute with Prof. K.B. Sharpless, he returned to Uppsala where he became Docent in 1994 and full Professor in 1999. Since 2010 he also holds the position of Honorary Professor at the University of KwaZulu-Natal, South Africa. As of January 2013, he is Professor of Organic Chemistry in Stockholm University. His main research interests involve organometallic chemistry, stereo-selective synthesis, and asymmetric catalysis.

Alban Cadu was born in 1987 in Rouen, France. He received a BSc from Imperial College London with Joint Honours in Chemistry with Management in 2010, his research focused on thiirane synthesis. In 2011 he joined Professor Andersson at Uppsala University, where he works towards a PhD, focusing on asymmetric organometallic substitutions of small organic molecules.

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